Metabolism

Definitions 2
Measurement of Metabolic Rate 3
Basal Metabolic Rate 3
Nutrition 4
Parenteral Nutrition (~TPN) 5
Catabolic & Anabolic Reactions 5
Oxidative Phosphorylation 7
Carbohydrate Metabolism 7
Protein Metabolism 11
Fat Metabolism 13
Starvation 17
Definitions

- calorie =
  - amount of heat energy necessary to raise temp of 1g water by 1 deg celcius eg 15 - 16 degrees
  - standard unit for heat energy
  - 1 calorie = 4.19 J
  - a kcal = 1000 calories
  - 1 calorie = 1 cal
  - 1000 calories or 1 kcal = 1 Cal
- metabolic rate = amount of energy liberated / unit of time
- total energy = external work + heat energy + energy stored
- Resp Quotient (RQ) = ratio of the volume of CO2 produced to volume O2 consumed / unit time at steady state:
  \[ \text{RQ} = \frac{V_{CO2}}{V_{O2}} \]
- **CHO**: RQ = 1 [H + O are present in same proportions as in H2O]
  - eg \( C_6H_{12}O_6 + 6O_2 \rightarrow 6 CO_2 + 6 H_2O + \text{energy} \)
  - thus RQ = 6/6 = 1
  - Undergoes complete oxidation in body → yield 4.1 kcal / g
- **Fats**: RQ = 0.7 (more O2 needed c/f CHO’s)
  - Undergoes complete oxidation in body → yield 9.3 kcal / g
- **Proteins**: RQ = 0.82 (more O2 needed c/f CHO’s)
  - Potentially 5.3 kcal / g, but undergoes incomplete oxidation → 4.1 kcal / g

- RQ gives an indication of preferred substrates or organs:
  - RQ for brain ~ 0.97 - 0.99 ie mainly CHO’s used
  - RQ stomach during acid secretion = negative ie uses more CO2
- Resp exchange ratio (R) = ratio of CO2 produced to volume O2 consumed / unit time **at any given instant** - ie doesn’t matter if equilibrium been reached
- R changes in diff situations:
  - ↑R:
    - hyperventilation
    - exercise
    - met acidosis
  - ↓R:
    - post exercise
    - met alkalosis
- energy balance = av adult must take in at least 2000 kcal/day to balance basal output ∴ allowing energy consuming tasks essential for life to continue
- oxidation =
  - combo of substance with O2
  - removal hydrogen
  - removal of an electron
  \[ \rightarrow \text{reduction} = \text{opposite of oxidation} \]
- oxidation reactions =
  - catalysed by specific enzymes
  - require
    - cofactors - ions
- coenzymes -
  - organic substances & non protein substances
  - are non specific
  - play accessory role as carrier products of O2 reactions
  - eg NAD & NADP ⇒ NADH + NADPH

**Measurement of Metabolic Rate**

- aka calorimetry
- direct method:
  - measures total amount of heat energy produced by body
  - pt in special insulated room
    - = Atwater-Benedict Chamber
  - MR = amount of energy/hr
- indirect method:
  - estimated by measuring VO2
  - MR ~ VO2 during aerobic metabolism
  - 4.82kcal/litre consumed
  - measurement:
    - use O2 filled spiometer with CO2 absorber in closed circuit
    - rate of ↓ circuit volume = proportional to VO2
    - slope of trace of volume vs time = VO2

\[
\text{VO2 (litre/hr) } \times 4.82 \text{ kcal} = \text{MR (kcal/hr)}
\]

usually given as per surface area: kcal/hr/m²

\[
\text{for norm VO2 of } \sim 250\text{ml O2/min 70kg person}
\]
\[
= 250 \times 60\text{mins}
\]
\[
= 15 \text{ litres /hr for}
\]

\[
\text{MR} = 15 \times 4.82\text{kcal}
\]
\[
= 72\text{kcal/hr / 1.8m²}
\]
\[
= 40\text{kcal/hr/m²}
\]

\[
\text{MR (kcal/kg/day)} = 28 = 70\text{kg person } \sim 2000\text{kcal/day}
\]

**Basal Metabolic Rate**

- = Metabolic rate measured at defined conditions:
  - at rest
  - at room temp
  - 12-14hrs after last meal
- It is not true basal rate cos is lower during sleep
- gives reproducible & standardised values
- results adjusted for age, sex, surface area/size
- reported as % above/below an age adjusted standard value derived from studies in healthy period
  - = basal = standard conditions
- effects on BMR:
  - ↑14% for each 1 deg ↑ temp
  - ↓ with starvation
• Norm BMR = 28Kcal/kg/day or 2000kcal/day

**Nutrition**

**Summary Needs**
• BMR = 28Kcal/kg/day
• water 30ml/kg/day
• protein = 1g/kg/day
• fat 50g/day
• CHO used to meet rest of calorie needs
• K & Na = 1mmol/kg/day

**Optimal Diet**
• Water ~30-40ml/kg/day average
• adequate:
  • calories - to meet BMR & extra = 30-kcal/kg/day
  • protein - dietary essentials
  • fat - essential FAs
  • electrolytes & minerals
  • nitrogen - 0.2g/kg
  • vitamins

**Calories**
• BMR 2000 kcal/day (28kcal/kg/d) for BMR + extra 500-2000kcal/day depending on:
  • activity
  • fever
  • illness
→ .: average 2800kcal/day
• to calculate dietary needs:
  - 1st: calculate protein needs
  - split remaining calories between fats & CHO depending on economic, taste factors
→ usually ~40-50% CHOs

**Protein**
• ~1g/kg/day of gd 1 proteins ie animal source
• grade 2 protein =
  • plant proteins
  • some lack one or more essential aa’s
• 70g/d of 70kg man = 280kcal/d from protein

**Fat**
• =most compact form of calories (9.3kcal/gram)
• high unsaturated/saturated ratio = good for preventing atherosclerosis
• unsaturated essential FAs = linolenic, linoleic + arachidonic
• +/-50-60g/day = ~600kcal/day

**CHO**
• meet rest of caloric needs
• ie 2800 - (280+600) = 1920 kcal/d

**Minerals**
• electrolytes (daily needs in mmol/kg/day):
  • Na = 1
  • K = 1
• \( Cl = 1.5 \)
• \( Ca = 0.1-0.2 \)
• \( Mg = 0.1-0.2 \)
• \( PO_4 = 0.2-0.5 \)
- essential trace elements eg arsenic, chromium, cobalt, copper, fluoroide, iodine, iron (0.2mg/kg/day), zinc (0.2mg/kg/day), manganese, nickel ,selenium

Vitamins
- = any dietary organic constituent necessary for life, health & growth that does not function by supplying energy
  - water soluble = B complex & C
  - fat soluble = A, D, E, K

Parenteral Nutrition (~TPN)
- aims are to prevent malnutrition
- used when:
  - GI tract not working
  - GI danger
  - GI needs rest
  - not possible to establish enteral route

Goals
- meet calorie needs 25-30kcal/kg/day
  - ↑ if burns/septic/fever
  - ↓ if ventilated/sedated
- CHO:
  - mixture glucose:lipids 50:50
    - max 4mg/kg CHO to prevent thermogenic response & ↑CO2 production
  - aim to ↓GNG & ↓lipolysis
  - stim insulin secretion
- lipid:
  - 1-2kcal/ml energy dense emulsion
- amino acids:
  - 1g/kg/day (more in burns)
    - substrate for protein synthesis
    - prevent proteolysis .. GNG
    - essential & non essentials given
    - glutamine added to maintain gut integrity
- electrolytes:
  - Na & K = 1mmol/kg/day
  - Mg + Ca = 10-15mmol/day
  - \( PO_4 = 20-40 \) mmol/day
- volume: according to losses incl insensible losses
- vitamins: all incl zinc (immunocompromise), copper, selenium, vit D (osteomalacia)

Catabolic & Anabolic Reactions

Catabolic
- = energy production
- CHO, fat, protein broken down into elemental compounds by digestion
- further catabolism occurs in 3 phases
inhibitors of catabolic processes:
  • insulin
promoters:
  • glucagon
  • catecholamines
  • glucocorticoids
  • growth hormone

Phase 1
  • incomplete oxidation of elemental substrates
  • eg glycolysis of glucose (and some aa’s) or B oxidation of FFAs
  • occur in cytosol of cells anaerobically
  • release 1/3 of total energy
  • 3 major compounds usually involved:
    • acetyl-CoA
    • alpha-ketoglutarate
    • oxaloacetate
      ↦ also involved in phase 2
  • 3 minor compounds usually produced:
    • pyruvate
    • fumarate
    • succinyl CoA

Phase 2
  • complete oxidation of substrates from phase 1 in the citric acid cycle (CAC)
  • occurs inside mitochondria
  • produces:
    • CO2
    • 2/3 of energy
  • energy is usually conserved by reduction of certain compounds
    ↦ eg NAD⁺ ⇒ NADH + H⁺
    FAD ⇒ FADH₂
    reduction of flavoproteins on inner membrane of mitochondria
    small amounts of ATP

Phase 3
  • oxidative phosphorylation
  • where enzymes reduced in phase 2 (flavoproteins) gets re-oxidised with their conserved energy
    transferred to ATP (by phosphorylating ADP)
  • at last step:
    • H gets released as water
    • = crucial step where O2 combines with H (catalysed by cytochrome a-3)
    ↦ ∴ without O2 whole process (incl CAC) stops and energy can only be formed by phase 1
  process
  (cyanide inhibits cytochrome a-3)

Anabolic Processes
  • involve:
    • glycogen synthesis
    • GNG
    • fat synthesis & storage
    • protein synthesis
  • promoted by:
Oxidative Phosphorylation

See general cell physiology notes

**Significance of OP**

- high yield of ATP but requires some O2
- anaerobic pathway must consume v large quantities of glucose to produce similar ATP:
  - high energy consuming organs need oxygen
  - eg brain, kidney, liver
  - if switch to anaerobic unable to transfer enough glucose \( \therefore \) ATP depletion \( \Rightarrow \) death
- anaerobic produce lactate (x2/glucose) \( \Rightarrow \) lactic acidosis
  - in brain:
    - BBB prevents lactate diffusing out
    - lactate ions + H\(^+\) retaining in neuron \( \Rightarrow \) intracellular acidosis

**Carbohydrate Metabolism**

- diet CHOs = polymers of hexoses:
  - d- glucose
  - d-galactose
  - d-fructose
  \( \leftarrow \) most monosaccharides = d isomers (dextrose = d-glucose)

**Mechanism Overview**

- glucose enters cell
- phosphorylated to G-6-P by hexokinase
- additional enzyme to hexokinase in liver = glucokinase:
  - ↓ed in starvation & diabetes
  - ↑ed by insulin
- G6P fate:
  - glycogen synthesis - polymerized to glycogen for storage
  - glycolysis - to form pyruvate or lactate or both
  - (in liver only) dephosphorylated by G-6-Phosphorlyase \( \Rightarrow \) released into blood
**Glycolysis**
- occurs only in cytoplasm of cells
- glucose → pyruvate is anaerobic
- 2 possible pathways:
  - Emden-Meyerhoff =
    - cleavage of fructose 1,6,P2 to yield 2 trioses
    - yields 4mol ATP
  - Hexose monophosphate shunt
    - = direct oxidative pathway
    - oxidation & decarboxilation to pentoses
    - generates large amounts of NADPH
    - NADPH essential for many metabolic processes incl drug metabolism/detox via C-P450
- pyruvate then converted in mitochondria to acetyl-CoA
- other substrates:
  - fats can enter glycolytic pathway via glycerol conversion to dihydroacetone phosphate
  - glucose can be converted to fat via acetyl-CoA (but only 1 way : vice versa via this pathway not possible)
  - proteins -
    - enter via number of aa’s
    - into Emben-Meyerhoff pathway or citric acid cycle
    - aa’s get deaminated to intermediates
  - non-glucose molecules - can be converted to glucose via gluconeogenesis

**Anaerobic Glycolysis**
pyruvate + NADH ↔ lactate + NAD+
- NAD+ produced allows glycolysis to continue
- lactate ultimately inhibits rate limiting enzyme 6-phosphofructokinase
- fate of lactate - either:
  - fully oxidised locally - when O2 available again - yields NET 36 ATP (ie 38 - 2)
  - t/f to liver: gluconeogenesis to glucose where stored as glycogen
  - t/f for direct usage in heart/kidney
- tissues either:
  - lactate producers = any tissue but mainly skeletal mm, rbc, brain, GIT
  - lactate metabolisers = liver, kidney, heart
- Cori cycle = metabolism of glucose to lactate in 1 tissue (eg muscle) followed by conversion back to glucose in another (eg liver)

**Citric Acid Cycle (CAC)**
- sequence of reactions in which acetyl CoA is completely oxidised to CO2 & H+ 
- occurs in mitochon matrix only
- = common pathway for oxidation of CHO, fat & some aa’s ⇒ CO2 & H2O
- brief outline:
  - AcetylCoA condensed with oxaloacetate (4c) ⇒ citrate (6c)
  - 2 CO2s are spint off to regenerate oxaloacetate (4C)
  - 4pairs of H-atoms transferred (via NADH +H and FADH2) to flavoprotein cytochromes (electron transfer) chain
  - 12ATP + 4H2O created
- major entry into cycle = acetyl-CoA:
  - B oxidation of FA's
- glycolysis
- ketones - B-hydroxybutarate $\rightarrow$ acetoacetate $\rightarrow$ Acetyl CoA $\rightarrow$ enters CAC
- aa’s can enter directly into CAC as described above
- CAC requires O2 (cannot operate anaerobically):
  - O2 only used in last step of electron transfer chain
  - if no O2 NADH will accumulate and inhibit the CAC
- glycolysis to pyruvate occurs in all cytoplasm outside of mitochondria
- pyruvate enters mitochondria where metabolised to acetyl-Co-A
- OP occurs only in mitochondria on cristae (inner lamella)

**Energy Produced**

<table>
<thead>
<tr>
<th>Anaerobic path</th>
<th>Aerobic path</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose $\downarrow$ pyruvate $\downarrow$</td>
<td>Glucose $\downarrow$ pyruvate $\downarrow$ CAC / OP</td>
</tr>
<tr>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
</tr>
</tbody>
</table>

2 mol lactate + 2 mol ATP

6 CO2 + 6 H2O + 38 mol ATP

so, the ATP ratio = 1:19

![Diagram showing energy yield in anaerobic and aerobic conditions](image)
**Directional Flow Valves**
- = regulators of intermediary metabolism

1. Glucose entry into cells and glucose exit from cells
   - Hexokinase \( \rightarrow \text{Glucose 6-phosphate} \)
2. Glucose
   - Glucose 6-phosphatase \( \rightarrow \text{Glycogen synthase} \)
3. Glucose 1-phosphate
   - Phosphorylase \( \rightarrow \text{Glycogen} \)
4. Fructose 6-phosphate
   - Phosphofructokinase \( \rightarrow \text{Fructose 1,6-biphosphatase} \)
5. Phosphoenolpyruvate
   - ADP \( \rightarrow \text{ATP} \)

- most reactions freely reversible
- reactions described above require different enzyme or transport mechanisms to reverse thus = flow valves

**Factors Determining Plasma Glucose**
- plasma glucose = balance amount glucose entering blood stream & amount leaving it
- principal determinants:
  - dietary intake
  - rate enter into cells of mm, adipose tissue & other organs
  - glucostatic activity of liver:
- utilisation breakdown:
  - 5% glucose converted into glycogen
  - 30-40% converted to fats
  - rest metabolised immediately in tissues & organs
- starvation:
  - fasting \( \Rightarrow \) liver glycogen broken down & glucose added to bloodstream
  - prolonged fasting \( \Rightarrow \) glycogen gone \( \Rightarrow \) liver \( \Rightarrow \) gluconeogenesis from
    - amino acids 
    - glycerol
- diagram of note:
  - glucostatic function of liver
  - loss of glucose in urine

By Adam Hollingworth

Metabolism - 10
**Gluconeogenesis**
- = glucose production from non-CHO precursors from metabolism of fats & proteins eg
  - lactate
  - glycerol
  - pyruvate
  - some aas eg alanine, glutamate, histidine
- occurs mainly in cytoplasm of liver
  ↦ can also occur in kidney
- very similar to glycolytic pathway in reverse:
  - acetyl Co-A cannot convert back to pyruvate
  ↦ instead convert to oxaloacetate inside mitochondria

**Protein Metabolism**
- essential amino acids:
  - arginine
  - histidine
  - isoleucine
  - leucine
  - lysine
  - methionine
  - phenylalanine
  - threinine
  - valine
- normal diet = 1g/kg/day of grade 1 protein contains above 8 aa’s as well as others
- L-isomer are more impt than D-isomer in humans
- structure of amino acids:
  - primary = order of aa’s in peptide chain
  - secondary = spatial arrangement produced by twisting and folding eg a helix, B sheet
  - tertiary = arrangement of chains into layers, crystals, fibres
  - quaternary structure = arrangement of subunits into functional structure

**Transamination**
- at level of common metabolic pool & citric acid cycle
- = conversion of 1 aa to corresponding keto-acid & simultaneous conversion of another keto-acid to aa
  ↦ eg Alanin (aa) + alpha-ketoglutarate (ka) ⇔ puruvate (ka) + glutamate (aa)

**Deamination**
- catabolism
- oxidation deamination occurs in liver

\[
\text{Aa} + \text{NAD}^+ \rightarrow \text{iminoacid} + \text{NADH} + \text{H}^+ \quad (= \text{dehydrogenation})
\]
\[
\text{Iminoacid} + \text{H}_2\text{O} \rightarrow \text{ketoacid} + \text{NH}_4^+ \quad (= \text{hydrolysis})
\]
\[
\text{NH}_4^+ \leftrightarrow \text{NH}_3 + \text{H}^+ \quad (\text{fwd reaction = in kidney and reverse = in brain})
\]
(Note: NH$_3$ = ammonia and NH$_4^+$ = ammonium)

**Amino Acid Cycle**
- ketogenic aas ⇒ converted to acetoactate:
  - tyrosine
- isoleucine
- leucine
- phenylalanine

- gluconeogenic aa’s:
  - alanine
  - tryptophane
  - serine
  - threonine
  - cysteine
  - glycine
  - glutamate

**Urea Formation**
- most of NH4+ formed by deamination of aa’s in liver ⇒ convert to urea in liver THEN renally excreted

**Nucleic Acids**
- Purines: adenine, guanine, hypoxantaine, xantine
- Pyrimidines: cytosine, thymine, uracil
- Nucleosides: = Purine / pyrimidine + ribose
- Nucleotides: = nucleoside + phosphoric acid residue
- Nucleic acids: =
  - helices formed from the nucleotides (eg double helix DNA)
  - RNA = ribonucleic acid (contains ribose)
  - DNA = deoxyribonucleic acid (contains deoxyribose).
- Nucleoproteins: Nucleic acid + one or more basic proteins

- Nucleic acids in diet → digested → constituent purines + pyrimidines get absorbed.
  - but most purines + pyrimidines are synthesised from aa’s in liver
- RNA is in dynamic equilibrium with the aa pool.
- DNA = metabolically stable through life once formed.

- Purines + pyrimidines released from metabolism of nucleotides may be (either)
  - re-used
  - catabolized:
    - Purines → URIC ACID
    - Pyrimidines → CO2 + NH3
  - (Minor amounts excreted unchanged in urine).

**Protein Degradation**
- = controlled process
- binding of proteins with ubiquitin ⇒ degraded
- ubiquitin:
  - highly conserved small regulatory protein which found in all eukaryotes
  - functions:
    - labels proteins for proteasomal degradation (most impt)
    - controls stability, function, intracellular localisation of many proteins
- uric acid:
  - created from
    - metabolism of purines
    - synthesised from eg glutamine
• removed in kidney:
  - filtered
  - 98% reabsorbed
  - 2% not reabsorbed ⇒
  • 20% excreted
  • 80% secreted

**Nitrogen Balance**
• v little protein loss in stool
• protein in diet (1g/kg/day) = nitrogen in urine

Eg: ↑ protein diet → ↑ deamination of aa’s → ↑ NH₄⁺ → ↑ urea + ↑ urinary urea = balanced.

• Negative balance:
  • eg starvation, DKA, (also: lack of essential aa’s in diet)
  • ↑ catabolic hormones from adrenal cortex (cortisol) & ↓ insulin
  • ⇒ urinary N2 > diet intake
• positive balance
  • eg growth, recovery illness, anabolic steroids

**Fat Metabolism**

**Essential FA’s**
• linoleic acid
• linolenic acid
• arachidonic acid
  ⊳ are polyunsaturated

**Fatty Acid Synthesis & Oxidation**
• all FA’s have an even no of C atoms
• if there are no double bonds = saturated
• double bonds (dehydrogenated) = unsaturated
  ⊳ poly unsaturated = many double bonds

• FA + glycerol ⇒ triglyceride
• many tissues can synthesise FA from acetyl CoA:
  • microsomes (outside mitochon): acetyl CoA ⇒ FA
  • inside mitochon - short chain FAs ⇒ long chain FAs
• can also be synthesised from aa’s & glucose
• max length synthesised FA = 16C
• in fat depots: FA + glycerol ⇒ neutral fats
  ⊳ occurs inside mitochondria
**B Oxidation**

- FA’s activated (inside or outside mitochon) using ATP \(\Rightarrow\) ADP
- short + medium FA’s diffuse into mitochon
- long chain FA’s must combine with carnitin
- breakdown to acetylCoA in mitochondria:
  - serial formation of 2C fragments
  - Acetyl-CoA can then enter CAC
- high yield of energy:
  - 1mol FA (6C) \(\Rightarrow\) 44mol ATP
  - glucose 38ATP; anaerobic glycolysis = 2ATP
- entails higher VO2 & RQ = 0.7 & 9.3kcal/g/fat

**Ketone Bodies**

- in many tissues acetylcoA condenses to form acetoacetyl-CoA
- only liver contains enzyme deacetylase
- acetocetate transformed to B-hydroxybutarate + acetone
- liver cannot catabolise these ketone bodies \(\Rightarrow\) circulation \(\Rightarrow\) oxidised by tissues eg mm in CAC
- if glucose pathway of B oxidation or fat pathway not supplying enough acetylCoA to CAC:
  - acetylCoA accumulates \(\Rightarrow\) condensation to acetoacetylCoA \(\Rightarrow\) ketone body formation in liver
  - ability of tissues to oxidise ketone bodies is soon exceeded \(\Rightarrow\) ketosis/ketonuria
  - acids initially buffered but will \(\Rightarrow\) acidosis
  - acetone discharged in urine & expired air
- 3 main causes for ↓intracellular glucose supply:
  - starvation
  - high fat, low CHO diet
  - DM
  \(\leftrightarrow\) \(\therefore\) CHO = antiketogenic in starvation and low CHO diet (NOT DM)
Brown Fat
- more in infants
- brown fat cells:
  - contain small fat droplets
  - well SNS innervated
  - ↑mitochon
  - uncoupling between metabolism & generation of ATP ⇒ ↑heat production due to ‘short cut’ of proteins back into matrix
- ∴ ↑SNS ⇒ ↑heat production

Plasma Transport of Fats
**exogenous system**
- FFA’s provided to tissues + fats cells from intestine by
  - chylomicrons = v large lipoprotein complexes
- Lipoprotein complexes: transport:
  - cholesterol
  - triglycerides,
  - phospholipids

**endogenous system**
- system made up of
  - VLDLs -
    - from liver
    - transport TGs, FAs, CHO made in liver ⇒ tissues
  - IDLs -
    - created when LPL removes most of triglyceride
    - become LDL when lose most of TG & protein in liver
- LDL - provide cholesterol to tissues
- HDL - take cholesterol back to liver

FFA Metabolism
- also synthesised in fat deposits where they are stored
- FFAs circulate bound to albumin
- =major source of energy for many organs eg heart (65%)
- supply to tissues regulated by 2 enzymes:
  - Lipoprotein Lipase (LPL):
    - found on endothelial cells of capillaries
    - 2 main functions:
      - [creation of adipose tissue]
      - hydrolyses TGs in chylomicrons & VLDL ⇒ FFA’s & glycerol
        - FFA & glycerol then enter cell and reassembled into fats
        - removes FFAs from VLDLs using heparin as a cofactor
    - ↑action by feeding & insulin
    - ↓action by stress & fasting
  - Hormone sensitive lipase (HSL)
    - [breakdown of adipose tissue]
    - intracellular in adipose tissues
    - TGs ⇒ FFA + glycerol
- FFA then sent to circulation and to other tissues
- ↑ action by
  • GH
  • glucocorticoids
  • thyroxine (slow)
  • fasting & stress
- ↓ action by: feeding, insulin, PGs
- ∴ HSL & LPL provide opposite functions

**Cholesterol**
- found only in animals
- source - mostly animal fat & egg yolks
- functions:
  • precursor for steroid hormones & vit D
  • part of structure of cell membranes
  • precursor to bile acids
- production:
  • chylomicron-remnants take cholesterol to liver
  • (liver & other tissues can also synthesise own cholesterol)
  • reabsorption from faeces in intestine
- regulation of production:
  • cholesterol feeds back to inhibit own production via HMG-CoA reductase
  • ∴ diet input high ⇒ ↓ hepatic synthesis
- excreted in bile ⇒ faeces/bile acid
- transported from liver mostly in VLDL
- modulators of cholesterol:
  • thyroid hormones: ↑ LDL receptors ⇒ ↓ serum chol
  • oestrogen: ↑ HDL & ↓ LDL
  • resins: = bind bile acids ⇒ ↑ cholesterol diverted to bile acids
  • niacin: ↓ LDL & ↑ HDL
  • statins: inhibit HMG coA reductase ⇒ ↓ serum cholesterol
Starvation

**Early**
- 24-48hrs
- glucose stores exhausted within 6hrs
- glycogen stores in liver (70-100g) & mm (400g) rapidly exhausted by 24hrs
- order of energy substrates:
  - glucose
  - glycogen - glycogenlysis - from liver due to low insulin conc
  - lipolysis - FFA’s released from adipose
  - [minimal] Ketogenesis - small amounts of acetoacetate & B-hydroxybutyrate produced by liver from FFA’s
  - [minimal] gluconeogenesis - GNG - from lactate & glycerol mainly in liver (some in kidney)

**Intermediate (2-4 days)**
- after ~24hrs: glucose produced almost entirely by:
  - aa’s
  - glycerol from fat
- lactate from rbcs
- ↑alanine =
  - most impt aa for GNG
  - works via alanin-glucose cycle
  - formed mostly in mm by
    - oxidation of isolecine, leucine & valine ⇒ pyruvate
    - then transamination of pyruvate
- ↑GNG coincides with 24-48hrs
  - ↑plasma glucagon - peaks at ~4days
  - ↓insulin
- Fat metabolism:
  - ↑plasma cortisol & adrenaline ⇒ ↑HSL ⇒ ↑mobilise fat stores ⇒ glycerol & FFAs
    - also ↓protein synthesis in skeletal mm
  - oxidation of FFAs ⇒ ↑serum B-hydroxybutyrate & acetacetate
- GH rises over 24-48hrs then declines

## Prolonged >4days

- ketone bodies gradually replace glucose as fuel for brain & nervous tissue
  - other tissues may revert to using FFAs as energy source
- Ketogenesis:
  - formed by liver
  - maintained at high rate
- GNG rate reduced as a protein sparing mechanism (due to ↓glucagon)
- s-glucagon ↓ed to prefasting levels at ~10days
- 1st week:
  -
- >2weeks:
  - insulin level remains low
  - serum cortisol & adrenalin ↑ing
  - protein breakdown
    - 1st week: ~75g/day
    - by week 3: ~20g/day due to Ketogenesis
• with prolonged fast metabolic rate ↓s by ~30% due to fall in mass of active tissue eg liver, kidney, GIT